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Risk Factors for Endometrial Lesions Detected by Hysteroscopy in Breast Cancer Patients Taking Tamoxifen

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Risk Factors for Endometrial Lesions Detected by Hysteroscopy in Breast Cancer Patients Taking Tamoxifen

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【**Abstract**】 **Background** Breast cancer has become the most common malignant tumor threatening the health of Chinese women in recent years. The use of tamoxifen（TAM）has successfully reduced the recurrence and progression of estrogen receptor-positive breast cancer, however, it also increases the risk of endometrial lesions. **Objective** To explore the risk factors for endometrial lesions in breast cancer patients taking TAM, determine the optimal threshold value of endometrial thickness, and improve the positive detection rate of hysteroscopy. **Methods** Breast cancer patients taking TAM（20 mg/d）who underwent hysteroscopic endometrial biopsy admitted to the Department of Gynecology of the First Affiliated Hospital with Nanjing Medical University from January 2015 to January 2022 were retrospectively selected as the study objects and divided into the negative hysteroscopic endometrial biopsy group（normal endometrium）and positive hysteroscopic endometrial biopsy group（endometrial lesions including endometrial polyps, endometrial hyperplasia without atypia, endometrial atypical hyperplasia and endometrial carcinoma）. Clinical data of the patients were collected, including age, BMI, history of hypertension and diabetes, delivery times, presence of menopause and abnormal uterine bleeding/postmenopausal bleeding（AUB/PMB）, receiving of chemotherapy, duration of TAM treatment, use of gonadotropin-releasing hormone agonists（GnRH-a）, endometrial thickness, echo features of intrauterine lesions. Multivariate Logistic regression analysis was used to explore the risk factors for endometrial lesions in breast cancer patients taking TAM. The receiver operating characteristic（ROC）curve of endometrial thickness for predicting endometrial lesions detected by hysteroscopy was plotted, and the area under the ROC curve（AUC）and its 95%*CI* were calculated to determine the optimal cut-off value of endometrial thickness for receiving hysteroscopic surgery. **Results** The proportion of patients with AUB/PMB, duration of TAM treatment ≥ 24 months, intrauterine hyperechoic lesions and endometrial thickness in the positive hysteroscopic endometrial biopsy group were higher than those in the negative hysteroscopic endometrial biopsy group（$P<0.05$）. Multivariate Logistic regression analysis showed that AUB/PMB〔$OR=7.731$, 95%*CI*（1.949, 30.699）, $P=0.004$〕, endometrial thickening〔$OR=1.223$, 95%*CI*（1.091, 1.371）, $P=0.001$〕 and

intrauterine hyperechoic lesions〔*OR*=13.383, 95%*CI*（2.751, 65.103）, *P*=0.001〕were independent risk factors for endometrial lesions detected by hysteroscopy in breast cancer patients taking TAM. The AUC of endometrial thickness for predicting endometrial lesions detected by hysteroscopy in breast cancer patients taking TAM was 0.753〔95%*CI*（0.638, 0.868）, *P*<0.001〕, with the Youden index of 0.54, optimal cut-off value of 9.15 mm, sensitivity and specificity of 0.755 and 0.786, respectively. **Conclusion** The risk of endometrial lesions is increased in breast cancer patients taking TAM with AUB/PMB, endometrial thickness ≥ 9.15 mm suggested by ultrasound and intrauterine hyperechoic lesions, when the hysteroscopy and endometrial biopsy should be actively considered.

【Key words】 Breast neoplasms; Tamoxifen; Endometrial hyperplasia; Hysteroscopy; Endometrial lesions; Endometrial thickness; Risk factors

Breast cancer is the top malignant tumor threatening women's health in China. The incidence rate of breast cancer in Chinese women has been on a continuous upward trend from 1990 to 2019[1], of which 50%-60% of patients are estrogen receptor （ER） positive. Endocrine therapy is suitable for almost all ER and/or progesterone receptor （PR）-positive breast cancer patients, which can effectively reduce the recurrence rate and improve the survival rate, among which tamoxifen （TAM） is widely used. TAM has both anti-estrogenic and weak estrogenic effects. In breast tissues, TAM competitively binds to ER of target cells, generating anti-estrogenic effects, inhibiting the growth and metabolism of tumor cells, and effectively decreasing the risk of recurrence and death rate of breast cancer. However, TAM has a weak estrogenic effect on the endometrium, and long-term use of TAM can cause endometrial thickening and lesions, increasing the risk of endometrial cancer[2]. For breast cancer patients taking TAM, transvaginal ultrasound is often used to monitor the endometrium. Hysteroscopic endometrial biopsy is the gold standard for the diagnosis and treatment of endometrial lesions in these patients[3]. However, previous studies at home and abroad on breast cancer patients taking TAM under hysteroscopic endomyocardial biopsy showed that only 21.1%-42.3% of the patients with endometrial lesions were indicated by final pathology, resulting in a waste of medical resources [4-6]. Therefore, we retrospectively analyzed the clinical data of breast cancer patients taking TAM who underwent hysteroscopy and biopsy, explored the relevant influencing factors of endometriosis in these patients, determined the optimal standard of endometrial thickness in breast cancer patients taking TAM who needed hysteroscopic surgical intervention, and improved the positive detection rate of hysteroscopic surgery.

1 Subjects and Methods

1.1 Study subjects A total of 132 cases of breast cancer patients taking TAM （20 mg/d） who underwent

hysteroscopic endometrial biopsy admitted to the Department of Gynecology of the First Affiliated Hospital of Nanjing Medical University from January 2015 to January 2022 were selected for the study. Based on the pathologic diagnosis after hysteroscopic surgery, the patients were divided into 43 cases in the hysteroscopic endometrial biopsy-negative group （with normal endometrium） and 89 cases in the hysteroscopic endometrial biopsy-positive group （such as endometrial lesions, including endometrial polyps, endometrial hyperplasia not associated with atypia, atypical hyperplasia of the endometrium, and endometrial carcinoma）. Among the 89 patients with endometrial lesions, 72 patients （54.5%） had endometrial polyps and endometrial hyperplasia without atypia 10 cases （7.6%）, endometrial atypia and endometrial cancer 7 cases （5.3%）.

Inclusion criteria: （1） the diagnosis of breast cancer was in accordance with the "Breast Cancer Diagnostic and Treatment Guidelines and Standards of the Chinese Anti-Cancer Association （2021 Edition）"[7]; （2） endometrial biopsy was performed under hysteroscopy in the Department of Gynecology of the First Affiliated Hospital of Nanjing Medical University; （3） the endometrial pathology data were complete. Exclusion criteria: （1） lack of regular menstrual cycle before breast cancer treatment; （2） failure to standardize the use of TAM or taking the drug for <3 months; （3） taking exogenous estrogen before breast cancer treatment; （4） family history of malignant tumors of the colorectum, endometrium, and ovary; （5） use of anticoagulant and antiplatelet drugs or accompanying hematological system diseases; （6） incomplete clinical data. The study was reviewed and approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanjing Medical University （Ethics No. 2022-SR-655）.

1.2 Methods General information and ultrasound characteristics of patients were collected by means of the hospital electronic medical record database and telephone questioning of patients, including age, BMI, history of hypertension, history of diabetes, number of deliveries, whether they were menopausal[7], whether there was abnormal uterine bleeding/postmenopausal bleeding （AUB/PMB）, whether there was chemotherapy, and whether there were any other clinical data. PMB）, presence of chemotherapy, duration of TAM administration, use of gonadotropin-releasing hormone agonist（GnRH-a）, endometrial thickness, and echogenic features of the uterine cavity.

1.3 Statistical analysis Statistical analysis was performed using SPSS 23.0 software. Measurement data were tested for normality, and those conforming to normal distribution were expressed as（$\bar{x}\pm s$）, and comparisons between groups were made using the independent samples t-test; non-normally distributed measurements were expressed as M （P25, P75）, and comparisons between groups were made using the Mann-Whitney U rank-sum test; and counting

data were expressed as relative numbers, and chi-square test or Fisher's exact probability method was used. The Kruskal-Wallis H test was used for nonparametric tests of multiple independent samples. Multifactorial logistic regression analysis was used to explore the factors influencing the hysteroscopic detection of endometrial lesions in breast cancer patients taking TAM. The working characteristic （ROC） curves of subjects whose endometrial thickness predicted endometriosis detected by hysteroscopy were plotted, and the area under the ROC curve （AUC） and its 95% CI were calculated to determine the optimal cut-off value based on the Jordon's index （Jordon's index = Sensitivity + Specificity - 1）. Differences were considered statistically significant at $P<0.05$.

2 Results

2.1 Clinical data Comparison of AUB/PMB, TAM medication time, endometrial thickness, and intrauterine hypoechoic occupancy between patients in the hysteroscopic endometrial biopsy-negative group and those in the hysteroscopic endometrial biopsy-positive group, the differences were statistically significant （$P<0.05$）; the age of the patients in the two groups, BMI, history of hypertension, history of diabetes mellitus, number of deliveries, menopause, chemotherapy, GnRH-a, and intrauterine anechoic occupancy. Comparison of abnormal blood flow signals in the uterine cavity, the differences were not statistically significant （$P>0.05$）, as shown in table 1.

Table 1 Comparison of clinical data between the two groups of patients

Group	Case	Age〔M（P25, P75）, year〕	BMI（kg/m）	History of hypertension〔case（%）〕	History of diabetes〔case（%）〕	Number of deliveries〔M（P25, P75）, time〕	Menopausal〔case（%）〕	AUB/PMB〔case（%）〕	Radiotherapy〔case（%）〕
Hysteroscopic endometrial biopsy negative group	43	52（46, 54）	23.6±3.4	6（14.0）	0	1（0, 3）	29（67.4）	3（7.0）	24（55.8）
Hysteroscopic endometrial biopsy positive group	89	49（44, 52）	23.2±2.5	18（20.2）	5（5.6）	1（1, 1）	49（55.1）	25（28.1）	63（70.8）
Test statistic value		-1.046[a]	0.529[b]	0.766	1.206[c]	-1.940	1.840	7.733	2.893
P value		0.296	0.598	0.381	0.272	0.052	0.175	0.005	0.089

Group	GnRH-a〔case（%）〕	TAM dosing time〔case（%）〕		Endometrial thickness（mm）	Intrauterine hyperechoic cavity〔case（%）〕	Intrauterine echogenicity〔case（%）〕	Abnormal blood flow signal in the uterine cavity〔case（%）〕
		≥24 months	<24 months				
Hysteroscopic endometrial biopsy negative group	4（9.3）	20（46.5）	23（53.5）	9.49±3.79	2（4.8）	15（35.7）	1（2.4）
Hysteroscopic endometrial biopsy positive group	9（10.1）	58（65.2）	31（34.8）	12.44±4.66	30（33.7）	31（34.8）	10（11.2）
Test statistic value	0.021	4.175		-3.566	11.430	0.010	1.871
P value	0.884	0.041		0.001	<0.001	0.921	0.171

Notes: AUB/PMB=abnormal uterine bleeding/postmenopausal bleeding, GnRH-a= gonadotropin-releasing hormone agonist, TAM= tamoxifen; a indicates *Z* value, b indicates t value, c indicates the value of the test statistic using Fisher's exact probability method, and the residual test statistic is the χ^2 value.

2.2 Multivariate Logistic Regression Analysis of Factors Influencing the Detection of Endometrial Lesions by Hysteroscopy in Breast Cancer Patients Taking TAM The endometrial biopsy results of the patients' hysteroscopy （assigned value: negative =0, positive =1） were used as the dependent variable, and the statistically significant differences of the variables in 2.1 were used to compare the endometrial biopsy results of the patients' hysteroscopic endometrial biopsy results （assigned values: negative =0, positive =1）, the duration of TAM medication （assigned values: <24 months =0 The results of multifactorial logistic regression analysis with the variables AUB/PMB （assignment: no =0, yes =1）, time of TAM medication （assignment: <24 months =0, ≥24 months =1）, endometrial thickness （assignment: measured value）, and intrauterine hyperechoic occupancy （assignment: no =0, yes =1） as the independent variables showed that AUB/PMB, increased endometrial thickness, and intrauterine hyperechoic occupancy were the independent risk factors for hysteroscopically detected endometrial pathology in breast cancer patients taking TAM （P<0.05）. 0.05）, as shown in table 2.

Table 2 Multivariate Logistic regression analysis of the influencing factors for endometrial lesions detected by hysteroscopy in breast cancer patients taking TAM

Independent variable	β	*SE*	Wald χ^2 value	*P* value	*OR* value	95%*CI*
AUB/PMB	2.045	0.703	8.462	0.004	7.731	（1.949, 30.699）
TAM was used for ≥24 months	0.384	0.450	0.728	0.394	1.468	（0.608, 3.549）
Endometrial thickness	0.201	0.058	11.990	0.001	1.223	（1.091, 1.371）
Hyperechoic mass in the uterine cavity	2.594	0.807	10.328	0.001	13.383	（2.751, 65.103）

2.3 ROC curve of endometrial thickness for predicting endometriosis detected by hysteroscopy in breast cancer patients taking TAM The AUC of endometrial thickness for predicting endometriosis detected by hysteroscopy in breast cancer patients taking TAM was 0.753 [95%*CI*（0.638, 0.868）, *P*<0.001], and the Jordon index was 0.54, with an optimal cutoff value of 9.15 mm. with a sensitivity of 0.755 and a specificity of 0.786, as shown in Figure 1.

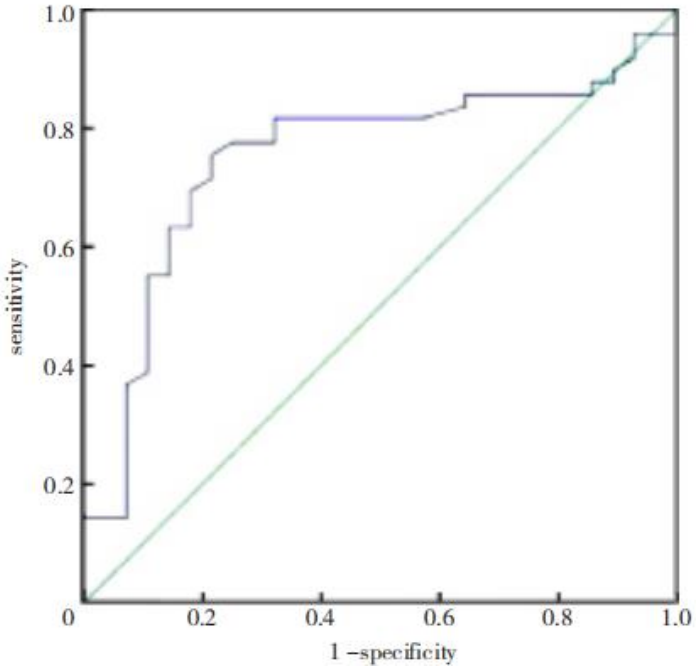

Figure 1 ROC curve of endometrial thickness for predicting endometrial lesions detected by hysteroscopy in breast cancer patients taking TAM

3 Discussion

The 2022 National Comprehensive Cancer Network guidelines further extend the duration of postoperative treatment with TAM from 5 to 10 years in patients with ER-positive breast cancer [8]. Previous studies of breast cancer patients taking TAM have shown that endometrial polyps are the most common type of endometrial lesion in breast cancer patients caused by TAM （8%-42%） [9], which is higher than in non-users （0-10%）[10]. Although endometrial polyps are benign lesions, TAM-associated endometrial polyps have a malignant rate of 3.0% to 10.7%, which is significantly higher than that of the general population（0.48%）[9], and still require active intervention. In Taiwan, a retrospective study comparing 39,411（53.1%） patients treated with TAM and 34,869（46.9%） patients not treated with TAM showed that the incidence rate of endometrial cancer in patients treated with TAM was 0.388%, while the incidence rate of endometrial cancer in patients not treated with TAM was 0.198%, suggesting that the use of TAM increases the risk of endometrial cancer in these patients[11]. Therefore, actively exploring the risk factors of endometrial lesions in breast cancer patients taking TAM, identifying the high-risk group as early as possible, strengthening monitoring and early intervention can reduce the risk of endometrial cancer. Some studies have shown a significant increase in the risk of endometrial cancer after 2 years of TAM use[12]. The results of this study showed that the proportion of patients in the hysteroscopic endometrial biopsy-positive group with TAM use for ≥ 24 months was higher than that in the hysteroscopic endometrial biopsy-negative group, but the relationship with endometrial lesions was not clarified, and more data are needed to verify this.

The results of this study showed that AUB/PMB was an independent risk factor for endometriosis detected by hysteroscopy in breast cancer patients taking TAM. A study of Korean women showed that abnormal uterine bleeding was associated with the development of endometriosis in breast cancer patients taking TAM[4]. A study by Pan Ningping et al[13] also showed that the presence of abnormal uterine bleeding was an independent risk factor for the development of endometrial cancer in breast cancer patients after surgery. The American College of Obstetricians and Gynecologists[14] and the Society of Obstetricians and Gynecologists of Canada[15] recommend hysteroscopy for breast cancer patients taking TAM with AUB/PMB. In the present study, the presence of AUB/PMB was strongly associated with positive endometrial biopsy results at hysteroscopy.

At present, ultrasonography suggests that endometrial thickening is an important indication of the need for hysteroscopic surgical intervention in breast cancer patients taking TAM. Since TAM can cause endometrial interstitial edema, which can result in ultrasonographic pseudo-thickening of the endometrium, there is no uniform clinical standard for the different criteria for endometrial thickness thresholds that require surgical intervention, and

for the positive rate of endometrial biopsy under hysteroscopy. SACCARDI et al[16] showed that in women taking TAM, the sensitivity of hysteroscopic endometrial biopsy for detecting endometrial lesions was 100% and the specificity was 15% when the endometrial thickness was 5 mm, and decreased to 84% and increased to 69% when the endometrial thickness increased to 10 mm. Other studies have shown that when the endometrial thickness cutoff value is 5-10 mm, the sensitivity of endometriosis detection is 85%-100% and the specificity is 56%-96%[17-19].

The results of this study showed that increased endometrial thickness was an independent risk factor for endometriosis detected by hysteroscopy in breast cancer patients taking TAM; and endometrial thickness had a certain predictive value for endometriosis detected by hysteroscopy in breast cancer patients taking TAM, with a sensitivity of 0.755 and a specificity of 0.786 for endometrial biopsy detection of endometriosis in hysteroscopic endometrial biopsies when the thickness of endometrium was 9.15 mm. The specificity was 0.786, similar to the above study.

The results of this study showed that intrauterine hyperechoic cavity was an independent risk factor for endometriosis detected by hysteroscopy in breast cancer patients taking TAM. HEREMANS et al[20] showed that ultrasound evidence of abnormal echogenicity in the intrauterine cavity was associated with endometrial polyps, endometrial hyperplasia, and endometrial carcinoma. HULKA et al[21] showed that in a study of postmenopausal breast cancer patients treated with TAM who had abnormal endomyocardial biopsies, the sensitivity and specificity were 0.755 and 0.86, respectively. The results of this study were similar to the above study. In a retrospective analysis of ultrasound findings in postmenopausal women with breast cancer treated with TAM, it was found that intrauterine hypoechoic occupations were closely associated with endometrial polyps, but were of limited value in determining the benignity or malignancy of endometrial lesions. The results of the present study are consistent with these studies.

In clinical practice, some mammologists choose to change the endocrine therapy regimen when endometriosis develops in breast cancer patients taking TAM. In this study, 23.5%（31/132） of patients changed their treatment regimen after the first hysteroscopy. Currently, there are 2 options for replacing TAM adjuvant endocrine therapy commonly used in premenopausal patients[7]: ovarian function inhibition + TAM, ovarian function inhibition + third-generation aromatase inhibitor （AI）, while postmenopausal patients are directly switched to AI therapy. It has been found that when breast cancer patients taking TAM are treated with the addition of the ovarian function inhibiting drug GnRH-a, serum estradiol levels and endometrial thickness can be significantly reduced[22]. The results of this study showed that patients in the hysteroscopic endometrial biopsy-positive group and the hysteroscopic endometrial biopsy-negative group were treated with GnRHH-a. The results of this study showed that there was no statistically significant difference in the use of GnRH-a between the hysteroscopic endometrial biopsy-positive group and the

hysteroscopic endometrial biopsy-negative group, which may be related to the fact that fewer patients used GnRH-a.

In conclusion, AUB/PMB, increased endometrial thickness, and intrauterine hyperechoic occupancy may be high-risk factors for endometriosis detected by hysteroscopy in breast cancer patients taking TAM. Breast cancer patients on TAM are at increased risk for endometriosis when they have AUB/PMB, ultrasound evidence of endometrial thickness ≥ 9.15 mm, and a hypoechoic occupancy in the uterine cavity. Hysteroscopy and endometrial biopsy should be actively considered.

Gynecologists need to consider the indications for hysteroscopic surgery in breast cancer patients taking TAM from multiple perspectives and factors, so as to reduce unnecessary surgical interventions, alleviate the economic burden on patients, and save medical resources. In addition, for breast cancer patients who have already developed endometriosis, gynecologists can communicate with breast doctors and patients themselves to weigh the pros and cons and formulate endometrial protection measures and change the endocrine treatment program.

Limitations of this study: firstly, this study is a single-center retrospective study with inherent flaws; secondly, the sample size of this study was small, and the risk factors included could not include all potential factors with diagnostic efficacy, for example, the small number of patients using GnRH-a in this study failed to obtain meaningful conclusions, and prospective studies in larger populations are needed to further validate the findings in the future.

Authors' contributions: Li Yujing proposed the research idea, was responsible for the conception and design of the study, the implementation of the study, and the writing of the paper; Jin Yichao, Chen Sheng, and Ji Mengying carried out the collection and organization of the data, the statistical processing, and the drawing and presentation of the graphs and charts; Jin Yichao revised the paper; and Dai Hui-Hua was responsible for the quality control and the review of the article, and was accountable for the article as a whole, and for supervising and managing the management.

There is no conflict of interest in this article.

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